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(72) Gisela Raether, Dipl.-Pharm.; Hans Wollmann, OPhR Prof. Dr. sc., German Democratic Republic

(73) see (72)

(74) Ernst-Moritz-Arndt University, Office for Innovator Mobilization and Patent Protection Rights, 2200 Greifswald, R.-Perershagen-Allee

(54) Process for the stabilization of pharmaceutical preparations with oxidation-sensitive components

(57) The process in accordance with the invention for the stabilization of pharmaceutical preparations with oxidation-sensitive components permits their industrial production by virtue of accomplishing the following tasks: firstly, significantly lengthening their periods of usability, e.g. up to 3 years for epinephrine eye drops; secondly, preventing discolorations that are due to the formation of colored decomposition products; thirdly, [conferring] very good stability properties under extreme conditions during manufacture, transportation, storage and use; and fourthly, [providing] the possibility of storage at room temperature. The stabilization process is based on combining at least three pharmaceutical ancillary substances - a discoloration protector, preferably sodium pyrosulfite, and an antioxidant, preferably N-acetylcysteine, and the complexing agent diethylenetriaminepentaacetic acid. The mechanism [of the process] is characterized by the following features: each individual component influences different causes of the decomposition process, whereby each on its own is only slightly effective, and two-fold combinations of these components exhibit, at the most, an additive or synergistic intensification of the effect, and a triple or multiple combination brings about a super-additive stabilizing effect. This is based, for its part, on mutual stabilization or, respectively, synergism of the individual components. [The process] is utilized in the pharmaceutical area, and has been put to the test for epinephrine eye drops as well as physostigmine eye drops and physostigmine eye salves.

11 pages

Title of the Invention

Process for the Stabilization of Pharmaceutical Preparations with Oxidation-Sensitive Components

Area of Application of the Invention

The invention pertains to a process for the stabilization of pharmaceutical preparations, as a result of which medicinal substances or ancillary substances, which are sensitive to oxidation or to induced decomposition, can be stabilized in pharmaceutical preparations such as solutions, salves, emulsions, suppositories and medicinal forms on the basis of polymers, etc.; as a result of this, significantly longer periods of usage are achieved.

Known Industrial Solutions [to the problems forming the basis of the invention]

Known industrial solutions are based on stabilizing the oxidation-sensitive active substance with the help of a stabilizer, which intervenes directly or indirectly in an oxidative degradation mechanism, or, respectively, with the help of combinations of a stabilizer and synergists that mostly possess no stabilizing properties themselves, but that assist the stabilizer in regard to its efficacy.

As a result, stabilization effects are produced over certain periods of time that are, in many cases, not sufficient for industrial production, especially when solutions [of medicinal preparations] are involved. In addition, the oxidation mechanism is not prevented from continuing via a different pathway, whereby this manifests itself, for example, by discolorations despite the stabilization procedure, or the desired stabilization effects no longer occur as a result of a change in the external or internal factors that affect stability, such as light, oxygen, the container, the temperature, the pH value, and buffering among other factors.

Discolored pharmaceutical preparations, whose active substance content no longer satisfies the requirements, or, respectively, those for which innocuous use is no longer possible because of an excessively high proportion, in particular, of toxic decomposition products, have to be discarded and cause economic losses. Known industrial solutions [to these problems] will be explained in more detail using the example of epinephrine hydrogentartrate in eye drops for the treatment of glaucoma. In the case of known industrial solutions for [the problem of] the stabilization of epinephrine in eye drops, use is made of stabilizers such as ascorbic acid, sodium pyrosulfite, 8-hydroxyquinoline sulfate, cysteine, N-acetylcysteine and erythorbic acid.

In the case of other known industrial solutions [to these problems], use is made of combinations of one of the designated stabilizers with synergists, whereby citric acid, tartaric acid and phosphoric acid are counted among these.

These routes for solutions exhibit periods of usability between 1 and 6 months at room temperature. It should be stressed in this connection that the determination of the active substance content is not permitted to take place by measuring the discoloration, and it is not permitted to take place with the help of a determination procedure that additionally measures the decomposition products that are

formed since higher active substance contents will otherwise be simulated. These routes to solutions are encumbered with the disadvantage that discolorations arise irregularly during the period of usage, especially [when the medicinal preparation is kept] in brown glass containers. Thus none of the known industrial solutions [to these problems] offers good prerequisites for industrial production in the case of epinephrine eye drops.

Objective of the Invention

The objective that forms the basis of the invention is to eliminate the shortcomings - such as influencing only one direction for the oxidative decomposition mechanism, irregularly occurring discolorations, low stability under conditions to which the medicinal agent can be exposed during manufacture, transportation, storage and usage - that are present in the case of known industrial solutions to the [aforementioned problems of] stabilization, and to permit their manufacture under industrial conditions by extending their inadequate periods of usability.

Essence of the Invention

In accordance with the invention, the problem of stabilizing oxidation-sensitive medicinal substances or ancillary substances is solved by the process of combining at least three pharmaceutical ancillary substances, whereby this process is based on the feature that the combination exhibits a super-additive stabilizing effect in the way that is described additionally below. In this connection, each of the individual components influences a different direction for the oxidative decomposition mechanism. The combination comprises a discoloration protector (e.g. sodium pyrosulfite), an antioxidant (e.g. N-acetylcysteine), and a complexing agent - diethylenetriaminepentaacetic acid (DTPA), whereby the mechanism of the effect is characterized by the following feature: each of the individual components is only slightly effective, and two-fold combinations of these components exhibit, at the most, an additive or synergistic intensification of the effect, and only the triple combination brings about a super-additive stabilizing effect.

The process additionally relates to the dependence of the intensity of the super-additive stabilization effect - based on the percentage decrease in the active substance that is to be stabilized - on the concentration of the individual components that has to be determined for each medicinal substance that is scheduled for stabilization. Concentrations that are above or below the concentration that is optimum for stabilization can be ineffective, or they can even act in a pro-oxidative manner. This task for the invention is accomplished appropriately for the practical example of epinephrine eye drops. The individual components or, respectively, the solution [to the problem] in its entirety in accordance with the invention possesses the following characterizing features:

Sodium pyrosulfite itself is not a stabilizer but, rather, a discoloration protector. It prevents the premature occurrence of discolorations that are produced as a result of oxidation and successively progressing reactions, even at very low concentrations of colored decomposition products. The loss in active substance itself is not affected. It [sodium pyrosulfite] acts as a synergist in combination with N-acetylcysteine, or with DTPA.

N-acetylcysteine preferably acts as an antioxidant. It is also capable of forming complexes to a slight extent. In the presence of sodium pyrosulfite, interactions occur in such a way that the antioxidant action of the N-acetylcysteine is intensified, and the discoloration protecting action of the sodium pyrosulfite is prolonged.

Diethylenetriaminepentaacetic acid (DTPA) is a chelating agent. It intervenes indirectly in the decomposition mechanism by binding metal ions, in the form of complexes, whereby these act as oxidation catalysts. Its action is synergistically intensified in the presence of sodium pyrosulfite. Other known chelating agents, e.g. EDTA, are significantly less effective, or are ineffective.

The action of the individual components, which has been described, is synergistically intensified by the process of combining sodium pyrosulfite, N-acetylcysteine and DTPA; as a result of this, pharmaceutical preparations, which have been stabilized in this way, with oxidation-sensitive medicinal substances or ancillary substances can be made to be super-additively usable for longer periods of time than in the case of stabilization with the help of only one or two components of the combination in accordance with the invention. An additional effect of the process in accordance with the invention comprises the feature that the stabilized preparation reacts in an essentially insensitive manner to factors that influence stability, such as light, air, oxygen, oxidation catalysts, the nature of the container, the storage temperature, the pH value, etc. The process in accordance with the invention also gives rise to the situation in which no discolorations are produced within the period of usability that has been achieved.

Example of an Embodiment

The process in accordance with the invention will be explained below by means of the example of epinephrine eye drops for the treatment of glaucoma.

Composition of the Epinephrine Eye Drops in Accordance with the Invention:

Variant I

1.	Sodium tetraborate	0.90 g
2.	Diethylenetriaminepentaacetic acid	0.01 g
3.	Boric acid	0.40 g
4.	Sodium pyrosulfite	0.30 g
5.	N-acetylcysteine	0.10 g
6.	Phenylethanol	0.50 g
7.	Epinephrine hydrogentartrate	1.00 g
8.	Water	to 100.0 g

pH value: 5.5-6.5

Variant II

1.	Diethylenetriaminepentaacetic acid	0.01 g
2.	Sodium pyrosulfite	0.30 g
3.	N-acetylcysteine	0.10 g
4.	Sodium chloride	0.60 g
5.	Phenylethanol	0.50 g
6.	Epinephrine hydrogentartrate	1.00 g
7	Caustic soda solution (40 g/l) to pH	5.5 - 6.5
8.	Water to	100.0 g

The decision regarding the preferred use of the buffered variant (I) or the non-buffered variant (II) requires a clinical test. The indicated stabilizer concentrations are optimal, whereby this has been ascertained specifically. Phenylethanol serves as a preservative.

Manufacture:

Variant I:
The [dis]solution of the components in a proportional quantity of water takes place in the sequential order 1.-8., whereby care is to be taken to ensure that the DTPA is dissolved in an alkaline medium only. Epinephrine hydrogentartrate is added to the pre-stabilized, additive-treated and preservative-treated solution, and then it is made up to 100.0 g with water. The finished solution is filtered in a bacteria-free manner and tapped off into sterilized vessels under aseptic conditions using gassing with an inert gas, if required.

Variant II:
The [dis]solution of the components takes place in the sequential order 1.-9., whereby care is to be taken to ensure that, first of all, the DTPA is dissolved in a small quantity of caustic soda solution. After all the other components have dissolved and the total quantity amounts to approximately 85-90 g, the mixture is adjusted to the indicated pH value with caustic soda solution, and then it is made up to the mark with water. Further treatment takes place as in Variant I.

Demonstration of the Super-Additive Effect:
In order to quantitatively determine the super-additive stabilizing effect with the help of the stabilization process in accordance with the invention, stressing tests were carried out at an elevated storage temperatur (40°C). They illustrate the improvement in the stabilizing action in %, i.e. the difference in the active substance contents of epinephrine solutions with and without stabilizing additions, and the percentage reduction in the rate of decomposition as a result of stabilizing additions in comparison to a pure epinephrine solution at the same pH value (Table 1).

In order to demonstrate the effects of the solution [to these problems] in accordance with the invention on the period of usability of the epinephrine eye drops, the results of the above-mentioned formulations are presented as a function of the [type of] container and gassing on a long-term [stability] test at room temperature (25°C), whereby a comparison is made with a selection of known industrial solutions [to these problems] (Table 2).

Table 1: Quantitative determination of the stabilizing action of 1% epinephrine hydrogentartrate solutions with stabilizing additions at 40°C

Addition	Improvement in the stabilizing effect in % 2 6 8 12 20 Days	Average	Reduction in the decomposition rate in % 2 6 8 12 20 Days	Average	Discoloration + 2 6 8 12 20	Estimate of the stabilizing effect
I Sodium pyrosulfite	0 0 0 0 -1	0	0 0 0 0 0	0	- - (+) + +	No stabilizer but, rather, a discoloration protector
II N-acetylcysteine	4 4 3 2 1	2.8	33 19 13 8 3	15.2	(+) + + + +	Antioxidant
III DTPA	2 2 2 1 2	1.6	17 9 8 4 7	9	+ + + + +	Complexing agent
I + II	9 13 14 10 12	11.6	75 61 61 41 38	55.2	- - - (+) +	Intensification of the effect via synergism
I + III	7 13 13 9 12	10.8	58 62 43 38 38	47.8	- - - + +	Intensification of the effect via synergism
II + III	6 6 5 3 4	4.8	50 29 22 12 12	25	(+) + + + +	Additive intensification of the effect
I + II + III	12 19 20 20 22	19	99 90 87 83 69	85.6	- - - - -	Super-additive intensification of the effect

+ - No discoloration (+) Sporadic discoloration + Discoloration

Table 2: Period of usability of the solution [to these stability problems] in accordance with the invention in comparison to known industrial solutions at a storage temperature of 25°C

Stabilization with	Period of usability (months) [*] Gassing with N2 in conventional commercial eye drop bottles comprising brown glass				Discoloration
	Au	Au'	PEND	N_2-[*]	
Process in accordance with the invention	18	24	24	36	None
Sodium pyrosulfite	1.5	2.5	2.5	-	Sporadically, irregularly
Sodium pyrosulfite + 8-hydroxyquinoline sulfate	3	4	4	6	Sporadically, irregularly
Ascorbic acid	2	3	3	-	Yes

Au Conventional commercial eye drop bottles comprising brown glass
Au' Eye drop bottles comprising brown glass of improved glass quality
PEND Containers comprising low density polyethylene

Invention Claim

1. Process for stabilizing pharmaceutical preparations with oxidation-sensitive components, characterized by the feature that a super-additive stabilization effect is achieved with the help of a combination of at least three pharmaceutical ancillary substances, as a result of which, firstly, the periods of usability of the pharmaceutical preparations are significantly lengthened, and, secondly, the valuable usage properties thereof are improved by preventing the occurrence of colored decomposition products.

2. Process in accordance with Point 1, characterized by the feature that the oxidation-sensitive components are medicinal substances or ancillary substances whose principal decomposition mechanism is oxidation, whereby other chemical reactions can proceed simultaneously or beforehand or thereafter, such as in the case of epinephrine, physostigmine or aminophenazone, for example.

3. Process in accordance with Point 1, characterized by the feature that the three ancillary substances for stabilization are a discoloration protector, an antioxidant, and a complexing agent that, for their part, influence different causes of the decomposition reaction.

4. Process in accordance with Points 1 and 3, characterized by the feature that the discoloration protector is preferably sodium pyrosulfite, and that the antioxidant is preferably N-acetylcysteine, and that the complexing agent is preferably diethylenetriaminepentaacetic acid (DTPA).

5. Process in accordance with Points 1, 3 and 4, characterized by the feature that the super-additive stabilizing effect is achieved via a combination of the designated ancillary substances, whereby each individual component is only slightly active and assistance of the specific activity property in each case ... by means of mutual stabilization or ... [sentence incomplete].

6. Process in accordance with Points 1, 2, 3, 4 and 5, characterized by the feature that the optimum concentrations of the designated ancillary substances (e.g. of the sodium pyrosulfite, and of the N-acetylcysteine, and of the DTPA) are separated in a suitable manner and have to be determined specifically for each pharmaceutical preparation as a function of the concentration of the active substance.

7. Process in accordance with Points 1, 2, 3, 4, 5 and 6, characterized by the feature that e.g. epinephrine eye drops for the treatment of glaucoma can be stabilized [thereby].

8. Process in accordance with Points 1, 6 and 7, characterized by the feature that concentrations of 0.3% sodium pyrosulfite, 0.1% N-acetylcysteine, and 0.01% DTPA are optimal for 1% epinephrine hydrogentartrate eye drops.

9. Process in accordance with Points 1 and 7, characterized by the feature that the manufacture of the stabilized epinephrine eye drops takes place in accordance with the sequential order that is defined in the example of an embodiment.